REMARKS

Claim Amendments

Upon entry of the foregoing amendment, claims 1-21 and 29-52 are pending in the application. Claims 1, 6, 8, 13 and 20 have been amended. Claims 29-52 have been added. Claims 22-28 have been canceled without prejudice or disclaimer to the subject matter therein. Support for the new claims can be found throughout the specification and in the claims as originally filed, and, in particular, at page 10, line 21 to page 13, line 26; page 15, lines 15-25; page 15 line 31 to page 16, line 5; and page 21, lines 4-8. Applicants respectfully request entry of the above amendment and submit that the above amendment does not constitute new matter.

Election/Restriction

The Office Action maintained the restriction requirement between Group I (claims 1-17) and Group II (claims 18-23). The Office Action states that the methods of Groups I and II present different steps and in particular, "one of the methods in Group II comprises applying a bacteriophage preparation to medical equipment...the steps in the method of Group I comprise treating a patient with a pharmaceutical composition." *See* O.A. at page 2.

Applicants agree that "one of the methods" in Group II (i.e., claims 21-23) comprises applying a bacteriophage preparation to medical equipment, but respectfully disagree that the other method in Group II (i.e., claims 18-20) presents different steps than that of Group I. For example, claim 17 (Group I) is directed to a method for reducing the incidence of infection by selected bacteria in a medical facility comprising administering a bacteriophage preparation which reduces the colonization level by bacteria (e.g., VRE) in patients at risk for infection by the selected bacteria. Likewise, claim 18 (Group II) is directed to a method for reducing the incidence of VRE infection in a medical facility comprising administering a bacteriophage preparation which reduces the number of VRE to patients at risk for VRE infection.[1] Accordingly, Applicants respectfully request that claims 18-20 be examined with Group I.

[1] Applicants note that the recitation of "in experimentally infected mice by at least 1 log" in claim 18 relates to the efficacy of the bacteriophage preparation and does not refer to a different method step.

Specification

Applicants have amended the specification to correct spelling and grammatical errors as suggested by the Examiner.

Claim Objection

Claim 6 is objected over the recitation of "MDSA." Applicants have amended claim 6 to recite "MDRSA" as suggested in the Examiner. Accordingly, Applicants respectfully request withdrawal of this claim objection.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 13-17 stand rejected under 35 U.S.C. §112, second paragraph, over the recitation of "who are admitted to said medical facility." Applicants have amended claim 13 to delete the recitation of "who are admitted to said medical facility." Claim 13 now recites a method for reducing the incidence of infection by selected pathogenic bacteria in a medical facility comprising administering to patients admitted to a medical facility a bacteriophage preparation which reduces the colonization level by the selected pathogenic bacteria in patients at risk for infection by the selected pathogenic bacteria. Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-17 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully disagree and traverse this rejection.

The Office Action states that the claims read on a broad genus of bacteriophage (and compositions thereof) comprising bacteriophage that have the ability to reduce the risk and incidence of infection by a broad genus of bacteria. *See* O.A. at page 4. The Office Action also suggests that the specification and the prior art do not describe phage that function to infect a broad range of specificity of host cells as that claimed. *See* O.A. at pages 5 and 6. The Office Action acknowledges, however, that the specification discloses several bacteriophages infect a broad host range of VRE. *See e.g.*, O.A. at pages 5 and 6.

Applicants agree that the claims are not limited to any particular bacteriophage, but submit that the claims do not require that each bacteriophage infect more than one species or serotype of pathogenic bacteria. Indeed, the effect of the recited bacteriophages is limited to the pathogenic

bacteria it lyses. Accordingly, Applicants respectfully disagree with the interpretation that the claimed invention requires that any bacterium can be treated with any lytic bacteriophage.

The specification and knowledge of one of skill in the art support a conclusion that Applicants were in possession of the claimed invention. Bacteriophage are well known in the art, as is their ability to target bacteria. *See e.g.*, "Background of the Invention" at pages 7-10. Methods of isolating bacteriophage and testing bacteriophage for host specificity are also well known. *Id.* As the Office Action acknowledges, the specification discloses several bacteriophages that infect a broad host range of VRE. *See e.g.*, O.A. at pages 5 and 6; *see also* Examples 2 and 3. Accordingly, one of skill in the art would understand that that Applicants were in possession of the claimed invention.

Applicants also note that the breadth of the dependent claims is further limited by elements such as patient population, specific bacteria, and both patient population and specific bacteria. For example, claims 3, 14, 19, 29, 31, 34, and 43 relate to immunocompromised patients and claims 8-9, 30, 38-39, and 44 relate to patients having a wound. Claims 5-6, 17-20, 29-31, 35-36, 43-50 and 52, for example, relate to specific bacteria. Claims 29-31, 34 and 38, for example, relate to both specific patient populations (e.g., immunocompromised or wound patients) and specific bacteria.

In view of the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph (written description) rejection.

Claims 1-17 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

Applicants respectfully disagree and traverse this rejection.

The Office Action provides a discussion of the *Wands* factors in view of the claimed invention. Applicants respond to each of the factors as set forth in the Office Action.

Nature of the Invention: Applicants generally agree with the Examiner's summation of the nature of the invention. Applicants note that several amendments and new claims have been added in this response. For example, Applicants have added new claims 32 and 51. Claim 32 relates to a method of reducing the level of colonization in a patient. Claim 51 relates to a method of reducing the risk that pathogenic bacteria will be acquired by persons in a medical facility.

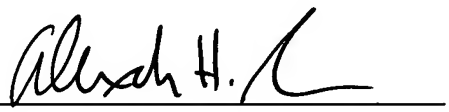
Breadth of the Claims: Applicants respectfully disagree with the Examiner's statement that "the claims are extremely broad because any bacterium can be treated with any lytic bacteriophage." O.A. at page 8. The claims do not state or suggest that any bacteriophage can infect any pathogenic bacteria. Indeed, the effect of the recited bacteriophages is limited to the pathogenic bacteria it lyses.

CONCLUSION

In view of the foregoing, Applicants respectfully request an indication of allowance of all claims.

Respectfully submitted,

HUNTON & WILLIAMS LLP

Dated: April 16, 2007 By: 

Laurence H. Posorske
Registration No. 34,698

Alexander H. Spiegler
Registration No. 56,625

HUNTON & WILLIAMS LLP
Intellectual Property Department
1900 K Street, N.W.
Suite 1200
Washington, DC 20006-1109
(202) 955-1500 (telephone)
(202) 778-2201 (facsimile)

infections. *See* O.A. at page 10 ("Although the rate of infection of the host cell range is very good, there are still 5% of VRE strains that remain viable and capable of causing nosocomial infection."). Applicants submit that given the teachings of the specification and the state of the art, an undue amount of experimentation would not be required to carry out the claimed invention.

In view of the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph (enablement) rejection.

risk of becoming infected, typically with their colonizing strain." Bradley, S. "Methicillin-Resistant *Staphylococcus aureus*: Long-term Care Concerns," The American Journal of Medicine (1999) 106: 2S-10S, at 3S, attached hereto as **Exhibit A**. Bradley cites to a study finding that "MRSA carriers were more likely to develop MRSA infections than non-carriers" and that "chronic carriers of MRSA were up to 10 times more likely to become infected with the colonizing MRSA strain." *Id.*

The claimed invention is not directed to treating individuals already infected with and showing symptoms of an illness caused by bacteria. Rather, the invention relates to administering bacteriophage prior to an individual developing an illness caused by pathogenic bacteria (e.g., when the individual is colonized by pathogenic bacteria). The administration of bacteriophages reduces the risk that the individual will be infected and develop an illness (e.g., a reduction in colonization will reduce the likelihood that a colonized individual will develop an illness).

Predictability and State of the Art: As discussed above, Applicants respectfully disagree with the Examiner's suggestion that the claimed invention is directed to preventing and/or curing any and all infections. *See* O.A. at page 9 ("Applicants *in vivo* mouse model, while showing a reduction in colonization of VRE, does not predictably indicate that the mice are no longer subject to infection by VRE i.e., the reduction in colonization *in vivo* does not necessarily indicate that the infection has been cured.").

To support its position, the Office Action cites to Barrow et al. The Office Action states that when chickens were treated with a bacteriophage at 1 and 2 days before an *E. coli* injection, only one out of seven chickens (<15%) died. *See* O.A. at page 9. The Office Action then asserts that the application of the bacteriophage did not reduce the risk of infection, since four out of nine chickens (44%) that were not treated with a bacteriophage died from the *E. coli* infection. *Id.* Applicants submit this argument is untenable because when the bacteriophage was applied, the fatality rate was significantly reduced from when the bacteriophage was not applied (<15% fatality rate compared to 44% fatality rate). Accordingly, Applicants respectfully submit the reliance on Barrow et al. is misplaced.

Applicants also disagree with the Examiner's conclusion that the art is highly unpredictable for the three reasons outlined in the first full paragraph on page 9. As discussed throughout the specification, bacteriophages are well known in the art, as is their mode of action and host specificity. As such, one of skill in the art would appreciate the use of bacteriophages in the claimed invention.

Amount of Experimentation: As discussed above, Applicants respectfully disagree with the Examiner's suggestion that the claimed invention is directed to preventing and/or curing any and all

Accordingly, because the claims do not cover any bacteriophage that can infect any bacterium, the breadth of the claimed invention is not "extremely broad."

Applicants also remind the Examiner that the dependent claims are directed to specific patient populations, specific bacteria, and both specific patient populations and specific bacteria. *See above.*

Working Examples and Guidance in the Specification: Applicants appreciate the Examiner's recognition of the teachings of the specification. In particular, the Office Action acknowledges the specification teaches that a cocktail of seven bacteriophages lysed 95% of 234 VRE isolates. *See* O.A. at page 8. The Office Action further acknowledges the specification teaches the direct inoculation of VRE infected mice *in vivo* resulted in at least a 1 log reduction of colonization. *Id.*

Applicants, however, disagree with the Examiner's suggestion that the claimed invention is directed to preventing any and all infections. *See e.g.*, O.A. at pages 8-9 (asserting that although 95% of VRE isolates were lysed and resulted in a reduction of colonization, the remaining 5% may infect an individual and cause medical problems). Indeed, the claimed invention directed to reducing the risk or incidence of bacterial infection, rather than preventing and/or curing any and all infections. *See e.g.*, claims 1 and 13; *see also* O.A. at page 8 ("the claims are directed to methods of reducing the risk or incidence of infection, as opposed to a method of treating.").

The Office Action acknowledges that "infection and colonization are distinct parameters." *See* O.A. at page 8. This distinction is important in understanding the claimed invention. For example, specification generally describes the relationship between infection and colonization as follows:

> The general rule is that patients first become colonized by pathogenic bacteria present in their immediate environment before developing illness due to those bacteria. Serious VRE infections, including septicemia, usually are preceded by intestinal colonization with the infecting organisms; therefore, the risk of septicemia is likely to be decreased by reducing colonization prior to periods when patients are severely neutropenic or otherwise immunosuppressed (i.e., reducing intestinal colonization may also reduce the risk of bloodstream invasion). The present inventors have discovered that certain strains of bacteriophage are particularly effective at lysing VRE. By administering these VRE-active bacteriophage to persons colonized with VRE, it is possible to substantially reduce or even eliminate VRE from the colonized person.

See page 15, lines 15-25; *see also* pages 3-6 (discussing the increased risk of illness due to colonization).

The state of the art has also recognized the relationship between colonization and infection. For example, Bradley states, "It has been long appreciated that carriers of *S. aureus* are at increased

Methicillin-Resistant *Staphylococcus aureus*: Long-term Care Concerns

Suzanne F. Bradley, MD

Colonization of residents of long-term care facilities with methicillin-resistant *Staphylococcus aureus* (MRSA) is an important healthcare concern. MRSA colonization is prevalent; in two of the most common sites of colonization, nares and wounds, colonization rates range from 8% to 53%, and 30% to 82%, respectively. With such a large number of patients harboring the organism, it is imperative that long-term care facilities are knowledgeable regarding the overall significance of MRSA, are aware of MRSA infection rates at their facilities, and have established a threshold above which outbreak precautions will be instituted. More importantly, facilities must ensure that appropriate precautions (e.g., hand washing, glove changes, gowns) are utilized to prevent transmission of MRSA to noncolonized residents. If these basic measures are taken, MRSA-colonized residents of long-term facilities should be able to be fully integrated into the everyday activities within the long-term care environment. In the event of an outbreak of MRSA infection, stricter isolation of colonized and infected residents is warranted, and such isolation should be discontinued as soon as the chain of transmission has been disrupted. Systemic antibiotics should be avoided in asymptomatic colonized patients; topical antibiotics like mupirocin should be reserved for short-term administration in outbreak situations. *Am J Med.* 1999;106(5A): 2S–10S. © 1999 by Excerpta Medica, Inc.

Methicillin-resistant *Staphylococcus aureus* (MRSA) first was identified in the United States at Boston City Hospital.[1] These initial MRSA isolates ultimately were traced to two debilitated elderly nursing home residents. Thus, the lore began that nursing homes were the reservoir for MRSA and, therefore, were responsible for the introduction of this resistant organism into the hospital setting. The belief that MRSA originated in long-term care (LTC) facilities was further supported by research by Hsu and associates,[2] who found that hospitalized patients with MRSA were more likely to have been admitted to acute care from nursing homes than from the community.

Infection with *S. aureus* is a significant problem in older adults in acute care. According to the Centers for Disease Control and Prevention, *S. aureus* is the second most common cause of bacteremia, soft tissue infections, and pneumonia in elderly patients in the acute care setting.[3] In addition, hospitalized elderly patients infected with *S. aureus* are more likely to die as a consequence of these infections than younger patients.[4]

Interest in the epidemiology of infection and its control in LTC has increased in the last decade, particularly as care has moved outside of the acute hospital care setting. The prevalence of *S. aureus* colonization and infection, primarily due to methicillin-resistant strains, has only recently been reported by approximately several dozen chronic care facilities worldwide. With the dramatically increasing number of elderly people, the group primarily occupying beds in LTC facilities, it is essential that the knowledge level increase. This article will outline what is known about the prevalence of MRSA in the LTC population, including risk factors for colonization and infection, appropriate infection control measures, and the use of antimicrobial agents to disrupt the spread of MRSA during outbreaks of infection.

EPIDEMIOLOGY

MRSA Colonization

Many of the available data regarding the prevalence of MRSA colonization were accumulated in Veterans Affairs facilities, and it is unclear whether these data may be extrapolated to community nursing homes. Unlike their Veterans Affairs counterparts, community LTC facilities generally treat an older patient population, have a greater percentage of women, and primarily provide unskilled or custodial care. The increased prevalence of resistant in-

From the Geriatric Research Education and Clinical Center, Department of the Veterans Affairs Medical Center, and the Department of Internal Medicine, Medical Center, University of Michigan, Ann Arbor, Michigan.

Requests for reprints should be addressed to Suzanne F. Bradley, MD, Ann Arbor Veterans Affairs Medical Center, Geriatric Research, Education and Clinical Center (11G), 2215 Fuller Road, Ann Arbor, Michigan 48105.

0002-9343/99/$20.00
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fections in Veterans Affairs LTC centers may be attributed to their close proximity to and frequent exchange of patients with acute care facilities.[5]

Colonization with *S. aureus* predominantly occurs at four sites: the nares, the skin, the rectum, and the perineum.[6] One study prospectively assessed the prevalence of colonization over 2 years in >500 residents of a Veterans Affairs facility in Ann Arbor, Michigan, a nursing home where MRSA infection was endemic.[5] The main sites of MRSA colonization in this patient population were wounds (e.g., vascular ulcers) and anterior nares. In the first year of the study, 23% of patients were colonized with MRSA; >40% of patients were colonized in wounds. The perineum and rectum were relatively uncommon sites of colonization (approximately 5%) among this patient population. During an epidemic of infection at a California rehabilitation hospital, colonization rates were even higher; 43% of patient nares and 82% of wounds were found to be colonized with MRSA.[7]

MRSA colonization rates in LTC facilities vary widely, ranging from 8% to 53% in nares, and 30% to 82% in wounds.[8] These surveys suggest that MRSA colonization in the LTC setting may be common.[5,7,9–16] Differences in colonization rates may depend on a variety of factors, including the size and location of the facility, the severity of illness of its residents, the prevalence of MRSA in referring hospitals, the presence of an outbreak of MRSA infection, and the infection control practices at the institution.

In a nursing home where MRSA was endemic,[9] cultures of resident nares, rectum, perineal skin, and wounds were obtained upon admission and monthly thereafter for 1 year. The mean length of stay in this facility averaged 3 months. Sixty-five percent of residents never acquired MRSA. A significant proportion of MRSA carriers, 25%, were already colonized upon transfer from the affiliated acute care hospital or from other institutions. Only 10% of residents acquired MRSA during their stay in the LTC facility. Once acquired, colonization with MRSA persisted in the majority (80%) of patients. Therefore, MRSA colonization may be common in LTC facilities because MRSA carriage persists, lengths of stays are long, and there is continued admission of patients already colonized from other facilities, in addition to the potential acquisition in the nursing home itself.

How efficiently is MRSA transmitted from resident to resident in the LTC setting? In the absence of an outbreak of MRSA infection, phage typing in one facility demonstrated a minimum of five phage groups colonizing nursing home residents. In only nine instances throughout the 1-year study were roommates colonized with MRSA found to harbor the same phage group.[9] Similar results were reported comparing MRSA antibiograms,[11] where, based on data from eight surveys administered during a 15-month period, MRSA transmission between roommates was felt to occur infrequently. Although newer molecular epidemiologic techniques were not done, these two studies suggest that the high rates of colonization in nursing homes could be due to the introduction of several clones into that facility, rather than dissemination of a single organism.

RISK FACTORS FOR MRSA COLONIZATION

All patients in nursing homes do not appear to be at the same risk of becoming colonized with MRSA. Results from multiple studies have provided clinicians with identifiable risk factors for MRSA colonization (**Table 1**).[5,9,11,15,17,18] They include diminished functional status, presence of foreign bodies (e.g., nasogastric tubes, intravenous catheters, urinary catheters), wounds, antibiotic therapy, and prior MRSA colonization. These risk factors are similar to those identified for patients in acute care facilities.

RISK FACTORS FOR MRSA INFECTION

It has been long appreciated that carriers of *S. aureus* are at increased risk of becoming infected, typically with their colonizing strain. Asymptomatic *S. aureus* colonization can occur in 10%–20% of healthy persons. Infection may ensue in the presence of some inciting event, such as a surgical procedure or underlying disorder such as diabetes or the need for dialysis. At the Veterans Affairs facility in Pittsburgh, Pennsylvania, Muder et al[13] found that MRSA carriers were more likely to develop MRSA infection than noncarriers. In this trial, patients who were chronic carriers of MRSA were up to 10 times more likely to become infected with the colonizing MRSA strain.

Which nursing home residents, then, are at risk of developing an infection with MRSA once colonized? The answer to this question is less clear. Terpenning et al[5] reported the presence of diabetes and peripheral vascular occlusive disease with an odds ratio of 5.1 and 4.3, respectively, as risk factors for developing MRSA infections in the LTC setting. The risk of death has been shown to be higher for MRSA carriers than noncarriers, but the increase in mortality could not be directly attributed to infection with MRSA itself. MRSA colonization is uncommon in the normal healthy host, and carriage may be a marker of increased debility.[13]

Prevalence of MRSA Infection in Long-term Care

Although asymptomatic MRSA carriage appears to be prevalent in chronic care facilities, the more important question is, how frequent is MRSA infection and what is the impact on patient morbidity and mortality? Six studies[7,9,13,14,16,19] have addressed MRSA infection in LTC facilities (**Table 2**).[5,9,11,15,17,20] In these six studies, data

Table 1. Risk Factors for Colonization by Methicillin-Resistant *Staphylococcus aureus* in Long-Term Care Facilities[5,9,11,15,17]

Category	Risk Factor
Patient characteristic	Bedridden or chair/bed confined status; poor functional status; male gender and urinary incontinence
Skin condition	Presence of wounds and decubitus ulcers
Invasive devices	Nasogastric intubation or intravenous catheter; feeding tube or urinary catheter
Prior antimicrobial therapy	Current antibiotic therapy
Prior colonization	Positive MRSA culture prior to prevalence survey

MRSA = methicillin-resistant *Staphylococcus aureus.*
Adapted with permission from *Infect Control Hosp Epidemiol.*[11,17,20]

Table 2. Methicillin-Resistant *Staphylococcus aureus* Infection in Nursing Homes

Study	Facility Size (No. of beds)	Total Admissions/ Patients Enrolled	Duration of Study (mo)	Total Infected Patients
Aeilts et al.[7]	600	18,379	29	28
Bradley et al.[9]	120	341	12	9
Muder et al.[13]	432	197	36	15
Mulhausen et al.[14]	120	421	12	7
Spindel et al.[19]	120	1,615	60	28
Storch et al.[16]	182	265	13	17
Total	1,574	21,218	162	104

Adapted with permission from *Drugs Aging.*[8]

have been collected throughout a period of time exceeding 10 years and encompassing >1,000 beds and >20,000 admissions. In all, just over 100 infections and five infection-related deaths were documented.[8] Overall, 41 of the 95 MRSA infections reported were soft tissue infections (**Figure 1**)[7–9,13,14,16,19]; rarely did patients require admission to an acute care facility for intravenous vancomycin. In a California facility,[7] urinary tract infections accounted for 11 of the 28 documented MRSA infections; these infections were linked to the use of urinary catheters, a potentially preventable risk factor for MRSA colonization. Similarly, in one facility,[16] 12 of the 18 MRSA pneumonias followed an influenza outbreak in a population with low vaccination rates. The breakdown of overall sites of infection is illustrated in Figure 1.[7–9,13,14,16,19] Therefore, although high rates of MRSA colonization lead to high rates of infection in the acute care environment, it has been suggested that serious infections caused by this pathogen occur less often in the LTC environment.

Would the introduction of MRSA into a LTC facility increase the overall rate of *S. aureus* infections? In one study conducted at a Veterans Affairs facility in Portland, Oregon,[20] a retrospective review of MRSA and methicillin-sensitive *S. aureus* (MSSA) infection rates was conducted among residents of the facility between January 1, 1988, and December 31, 1991 (MRSA introduced in December 1987). Results of this study revealed a transient increase in the overall *S. aureus* infection rate approximately 1 year after the introduction of MRSA to the facility. However, after this peak in 1989, infection rates once again declined to the baseline of approximately 0.3 infections per 1,000 patient days.[19] Results from studies in acute care facilities, however, have noted definite increases in the rates of *S. aureus* infections after MRSA introduction.[21,22] More information regarding the actual impact of MRSA on overall *S. aureus* infection rates remains to be delineated in the LTC setting.

Thus, it appears that MRSA colonization in the LTC setting may have different implications than in the acute care hospital. Current data suggest that some nursing home residents are at risk of becoming persistently colonized with MRSA, and some colonized residents will develop MRSA infection, generally infecting themselves with their colonizing strain. On the basis of the available reports in the literature, relatively few patients require hospitalization as a consequence of MRSA infection or die as a direct consequence. Chronic care facilities are very heterogeneous in their patient populations and care missions. More information is needed from different types of facilities from diverse geographic areas to understand fully the impact of MRSA on nursing home residents and how best to prevent infection in different settings.

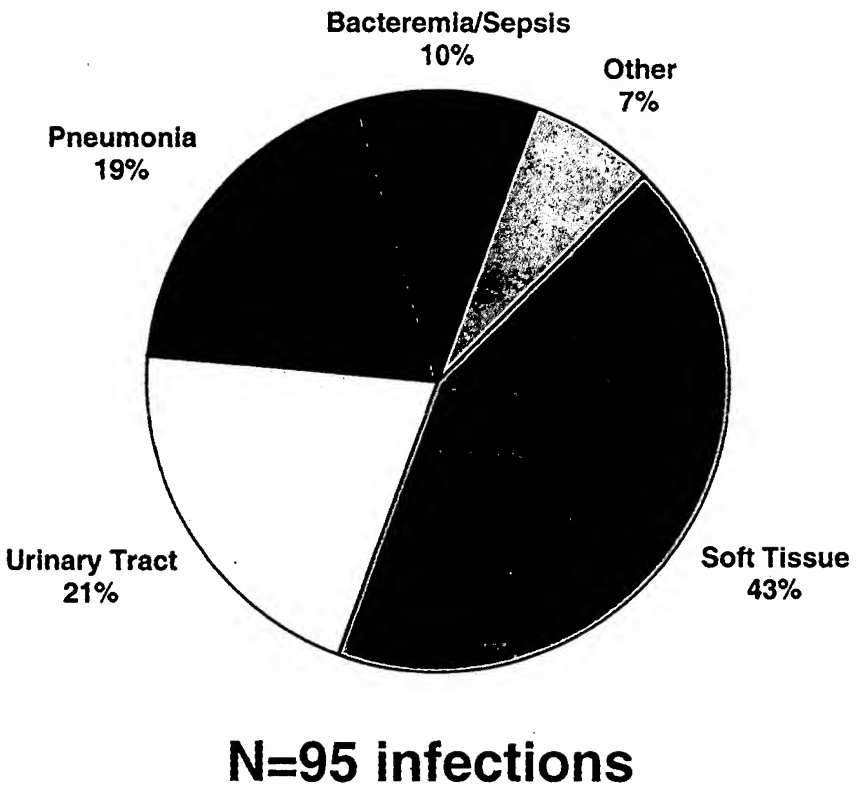

Figure 1. Sites and types of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in six studies of nursing homes.[7–9,13,14,16,19]

MANAGEMENT OF MRSA IN LONG-TERM CARE FACILITIES

Various techniques have been employed in an attempt to control colonization and infection with MRSA in LTC facilities, some with greater success than others. All LTC facilities should be aware of the importance of MRSA and should have a system in place to identify increases in infection rates (outbreaks) and a plan to prevent infection and control outbreaks. The following section outlines some basic strategies, including decolonization regimens and basic infection control practices for managing MRSA in the LTC environment (**Figure 2**).[8]

Infection Control Procedures

Appropriate infection control precautions are imperative for all healthcare settings to prevent the transmission of infectious agents among patients and healthcare workers. This practice is especially important in light of the current worldwide antimicrobial resistance problems. One major hindrance to the implementation of infection control practices at LTC facilities is the lack of resources for such programs. Few chronic care facilities have a full-time infection control practitioner. Infection control in the LTC setting is often a part-time job handled by staff without formal or minimal training. Long-term residents cannot be isolated from others for the duration of their MRSA colonization, which may persist for months to years, and receive good psychosocial and rehabilitative care. Patient to nurse ratios also tend to be higher in LTC facilities, and healthcare technicians provide a great deal of bedside care. Therefore, to be effective, infection control procedures must be simple to implement, recognize staffing and budget constraints, and realize that the patient care missions of nursing homes are quite different when compared with acute care facilities. Failure to develop effective infection control procedures that reflect the resources available in the LTC setting will likely result in the continued refusal of some nursing homes to accept patients colonized with MRSA or other antibiotic-resistant pathogens.

Surveillance

Most nursing homes do not have access to onsite microbiology laboratories, nor budgets to perform routine surveillance for MRSA carriage or strain typing. Neither the American Hospital Association nor the Society for Healthcare Epidemiology of America recommend routine screening for MRSA colonization in nursing home residents in the absence of suspected outbreaks of infection.[20,23] Keeping a line-listing of patients who have been

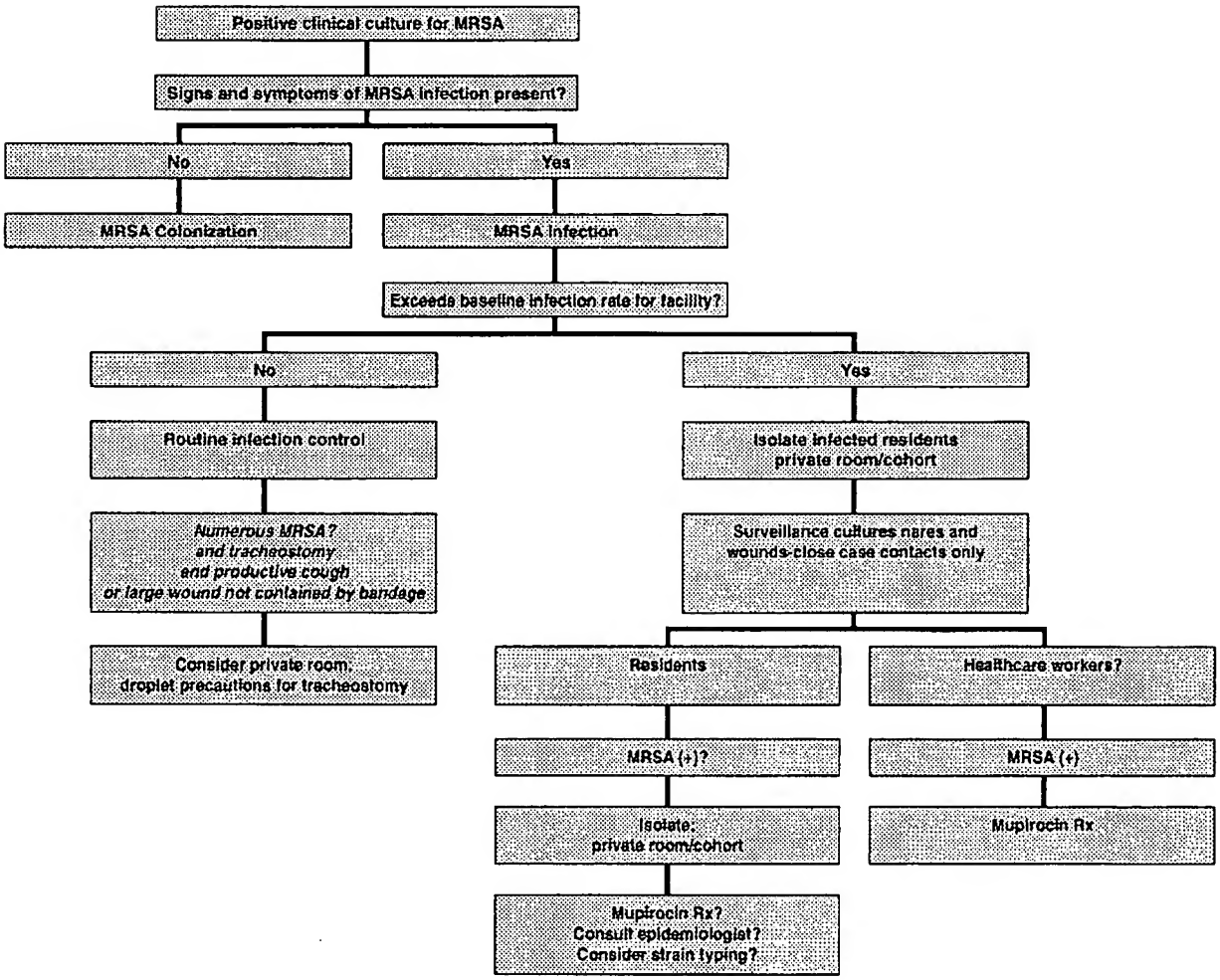

Figure 2. Infection control and methicillin-resistant *Staphylococcus aureus* (MRSA) infection in nursing homes. (Reprinted with permission from *Drugs Aging*.[8])

identified as MRSA carriers in hospital, or incidently by cultures obtained for clinical reasons, may be useful information in the event of an outbreak of infection. In fact, if MRSA carrier status is known, that information should be made readily available to the accepting facility upon transfer to hospital or nursing home, but not for the purposes of exclusion. Many nursing homes are not utilizing clinical cultures obtained for other purposes that are readily available to identify residents who have MRSA in their facilities. Thurn et al[24] found that only 7% of Minnesota LTC facilities routinely assessed cultures already obtained for clinical reasons for the presence of MRSA.

To establish whether MRSA is a problem, nursing homes need to determine if symptomatic infection with MRSA is occurring and how often. Are rates of MRSA infection per month or per 1,000 resident-care days increasing, decreasing, or remaining stable for a given chronic care facility? An individual nursing home needs to determine, based on prior infection rates, what number of cases of MRSA infection would lead the facility to declare an outbreak, utilize more intensive infection control techniques, and more resources to identify the source and contain its spread. In facilities where collection of baseline infection rates is difficult or not available, baseline data from a similar facility may be used for comparative purposes,[25] although this method is not ideal.

Precautions

MRSA most commonly is spread to patients by direct contact with the contaminated hands of personnel. Washing hands between contact with residents is most important in preventing the spread of bacteria by direct contact.[23] Whether the use of antimicrobial soap is more effective than standard soap in reducing transmission of MRSA has not been proven in this setting.[23] Changing gloves between patients and wearing gowns when there is a risk of contact with bodily secretions is also necessary (**Table 3**).[23] Significant improvement in infection control

Table 3. Keys to Controlling Methicillin-Resistant *Staphylococcus aureus* in Long-Term Care Facilities

- Provide staff education (e.g., significance of asymptomatic colonization versus infection)
- Obtain baseline data regarding infection rates at the facility
- Establish a threshold above which outbreak precautions will be instituted
- Practice appropriate standard precautions
  —Wash hands between every patient
  —Change gloves between every patient
  —Wear a gown if contact with secretions is anticipated
- Contain sites of MRSA colonization (e.g., wound dressing, urinary catheter)
- Isolate patients during outbreak situations
- Avoid the routine use of systemic antibiotics for eradication of MRSA colonization
- Use topical antibiotics like mupirocin for short-term control during outbreak situations

MRSA = methicillin-resistant *Staphylococcus aureus*.

in nursing homes is possible, because, according to current estimates, gloves are changed between patients only 27% of the time.[26] Wounds should be properly covered at all times with a dressing and bandage. Once MRSA-positive secretions are contained, residents should be free to go about their daily living activities within the institution.

Private Rooms/Cohorting

The routine use of private rooms or cohorting of MRSA carriers, which may be practical for some acute care facilities, is more difficult to implement in LTC institutions. Private rooms frequently are in short supply in the LTC setting. In addition, the use of cohorting and private rooms limits the number of beds available and can be costly to the LTC institution. Cohorting is an effective means of preventing the spread of MRSA during an outbreak of infection,[16,27] but its routine use impinges on the care of residents, limiting their daily activities and rehabilitation. In a study by Wenzel et al,[28] it was noted that colonization with MRSA may be prolonged, persisting for up to 4 years in one nursing home resident. Thus, in the absence of an outbreak of MRSA infection, routine cohorting, private rooms, and limiting patient movement has not been recommended, especially in facilities where endemic colonization rates approach 20%–30%, with the following exceptions[20,23]: Private rooms may be indicated for MRSA carriers with large, open wounds that cannot be contained by a bandage. Other instances that may warrant cohorting or private room placement include patients who are incapable of containing a cough productive of MRSA-positive secretions (tracheostomy) or those who are incontinent of urine.[29] Facilities that clearly know that their endemic rate of MRSA infection is low (<1 case/1,000 resident-care days) could attempt to screen all admissions for MRSA and cohort all carriers together if they had the resources to do so. Whether such a routine strategy is effective in preventing the introduction of MRSA into a facility with low prevalence has not been reported or shown to be cost effective.

Eradication of MRSA Colonization

Several approaches have been utilized in the attempt to eradicate MRSA colonization from healthcare facilities. In the acute care setting, the following three strategies have been used with varying degrees of success: (1) discharge MRSA carriers; (2) decolonize MRSA carriers; (3) disinfect the environment. Discharging all MRSA carriers from LTC facilities is not practical or feasible. Outbreaks of *S. aureus* infection have been traced to environmental sources infrequently, primarily in intensive care or burn units. In the few studies done in nursing homes, environmental MRSA strains may not necessarily correlate with the strains known to colonize patients.[9] Although disinfection is an important component of preventing the transmission of many bacteria, such as vancomycin-resistant enterococci or *Clostridium difficile*, it is not clear that special measures to clean the environment are effective in controlling the spread of MRSA.

Various oral antibiotics have been employed in an attempt to eradicate the MRSA carrier state or reduce the numbers of MRSA being shed. In one study conducted in a Veterans Affairs nursing home care unit,[30] 36 residents received one of three decolonization regimens. Patients who were colonized only in the nares received one drug (rifampin or trimethoprim/sulfamethoxazole) for 5 days; patients with more than one colonization site received two drugs for 5 days (rifampin plus trimethoprim/sulfamethoxazole, rifampin plus clindamycin, or trimethoprim/sulfamethoxazole plus clindamycin); and patients with instrumentation received two drugs for 10 days (rifampin plus trimethoprim/sulfamethoxazole). Before the initiation of drug therapy, 92% of the MRSA cases were documented as susceptible to rifampin; after the decolonization regimen, 43% of MRSA isolates were susceptible. Additionally, 56% of those treated remained colonized or became recolonized after therapy. In the acute care setting, recolonization and development of resistance have followed the extensive use of quinolones for MRSA carriage.[30] The widespread use of systemic antibiotics for decolonization of asymptomatic carriers of MRSA is not generally recommended. The armamentarium of effective agents to treat symptomatic MRSA infection already is limited; increased resistance induced by the treatment of asymptomatic MRSA carriers will compound these problems. Use of systemic antibiotics for carriage should be considered only in the context of an outbreak of MRSA infection to reduce the numbers of bacteria shed and decrease the likelihood of transmission to other patients.

Topical antibiotics also have been studied for eradica-

tion or decolonization of the MRSA carrier state. Mupirocin has been approved for decolonization of MRSA carriers during outbreaks of infection. Mupirocin has also been used to eradicate *S. aureus* colonization in hemodialysis and peritoneal dialysis patients with reduction in infection. Using a similar regimen, Veterans Affairs NHCU residents[31] were identified as being persistently colonized with MRSA in nares and/or wounds and were treated with mupirocin once daily for 7 days or 14 days, respectively. Treatment then was continued three times weekly for 3 weeks, followed by once weekly until a minimum of 3 months of consistently negative cultures were obtained. In this patient population, intranasal mupirocin administration resulted in an 83% microbiologic clearance rate after the first week. Simultaneous treatment of nares and wounds resulted in a 95% eradication of MRSA nasal colonization after 7 days. After 2 weeks of treatment, the nares of virtually every resident were negative for MRSA. However, treatment of nares without treatment of wounds was not effective in eradicating MRSA wound colonization.

In contrast, Reagan et al[32] found that MRSA carriage was eliminated in nares and on the hands of healthy healthcare personnel following intranasal mupirocin application. Results of studies examining the effect of intranasal mupirocin application on MSSA colonization in hemodialysis patients demonstrated similarly positive eradication rates.[33,34] Unfortunately, unlike the results in hemodialysis patients, weekly mupirocin therapy was not sufficient to prevent recolonization with MRSA in the Veterans Affairs patient population. Thirty-eight percent to 40% of nursing home residents experienced a recurrence of MRSA colonization. Thus, topical treatment with mupirocin in nares and wounds effectively reduced the overall colonization rate in the facility from a baseline of 23% to 11%, but MRSA colonization was not eliminated. It is entirely possible that approximately 5% of the residents recolonized their nares or wounds from untreated sites, such as the rectum. However, intensive attempts to eliminate MRSA colonization did not reduce or eliminate MRSA infection, perhaps because the rates of MRSA infections in the facility were already low before mupirocin therapy was instituted.[9] Furthermore, mupirocin resistance (mostly low level) was induced in 11% of patients.[31]

A follow-up study was conducted at the same facility[35] examining the effect of a 14-day treatment regimen with intranasal mupirocin in 14 patients and laboratory employees known to be colonized with MRSA or MSSA. At the end of the 14-day treatment period, virtually every patient in the study had high-level mupirocin-resistant coagulase negative staphylococci in their nares; many also were colonized with enterococci. Therefore, although the *S. aureus* was eradicated in most persons treated, the study population was colonized with new, drug-resistant organisms.

Outbreak Management

If an outbreak, defined as an increase of MRSA infection rates >25% above the preestablished threshold,[25] should occur, isolation and/or cohorting of MRSA-infected LTC residents and reinforcement of infection-control procedures are appropriate measures.[8] In the setting of an epidemic of MRSA infection, close contacts with MRSA-infected individuals should be surveyed for MRSA colonization. MRSA colonized patients who are close contacts of MRSA infection cases should be isolated, and MRSA-positive healthcare workers should be decolonized, generally with a topical agent.

Healthcare workers who are MRSA positive and who are involved in the care of an affected patient may be treated with intranasal mupirocin twice daily for 5 days; this therapeutic regimen should decolonize most carriers of their MRSA within 48 hours of initiation and will prevent the need to remove employees from work.[8] If no further MRSA infections occur, the chain of transmission is interrupted, and isolation precautions may be discontinued. If new infections are identified despite reinforcement of infection control procedures and cohorting, a brief course of mupirocin should be considered for decolonization of patients who are MRSA positive.

To track the MRSA outbreak effectively, the following data should be recorded: date of MRSA-positive culture, site/type of infection, location in facility, close contacts, contact with other MRSA-positive patients, and antibiotic sensitivity test results.[29] Some MRSA colonized residents will be placed in isolation and some residents and staff receive decolonization therapy unnecessarily because they carry MRSA strains that are different from the epidemic strain. Although molecular typing can help differentiate epidemic from nonepidemic strains, such tests may not be readily available to most nursing homes, and it may not be possible or practical to delay decisions to institute outbreak precautions while attempting to have strains typed or awaiting results.

However, with the assistance of a specialist in infectious diseases or infection control, molecular typing can be useful in delineating whether the increase in MRSA infections is really an outbreak as a result of the transmission of strains between residents and staff.

TREATMENT OF MRSA INFECTION

Clearly, the management of MRSA infections is limited by the small number of antibiotics with activity against these resistant strains. Until late in 1997, vancomycin was the only agent available with reliable activity against serious MRSA infections. Other agents, including doxycycline, fluoroquinolones, gentamicin, novobiocin, rifampin, and trimethoprim/sulfamethoxazole have been

used to treat patients infected with MRSA in an ongoing effort to expand treatment options. However, physicians have less clinical experience with these agents, the efficacy of these agents is not always optimal, and resistance to these agents has developed. Increasing resistance to quinolones[36–38] and rifampin[30] has been documented in the medical literature.

Quinupristin/dalfopristin (Synercid, Rhône-Poulenc-Rohrer, Collegeville, Pennsylvania), the first agent in the streptogramin antibiotic class, has been approved for the treatment of drug-resistant, gram-positive infections. It is the first antibiotic since vancomycin to offer potentially promising activity against MRSA.[39] In addition, another new antibiotic class under investigation, the oxazolidinone (Linezolid, Pharmacia-Upjohn, Bridgewater, New Jersey), may be useful for MRSA treatment.[40] Although the availability of these new agents offers hope, it remains to be seen how effective they will be with extensive use in practice.

CONCLUSION

Because MRSA colonization is likely common in nursing homes, especially in Veterans Affairs–affiliated facilities, it is important to manage it wisely. The main sites of colonization are nares and wounds, and the overall rate of colonization varies greatly among facilities. Transmission within the facility appears to be rare and can be avoided by emphasizing appropriate standard infection control procedures, such as hand washing. Antibiotic use for decolonization purposes, generally topical therapy, should be reserved for documented outbreaks of infection to prevent further transmission of MRSA and always should be administered short term to prevent the emergence of resistant pathogens. Clinicians should remember that despite best efforts to eradicate *S. aureus*, recolonization is common in chronically ill nursing home patients.

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